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Perfluorooctanoic acid: Relationship between repeated inhalation exposures and plasma PFOA concentration in the rat

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Abstract

A large database exists describing the pharmacokinetic behavior of perfluorooctanoic acid (PFOA) following oral exposure. The objective of this study was to examine the concentration- and time-dependence of the pharmacokinetics of inhaled PFOA in rat plasma to determine equivalent inhalation and oral (from literature values) exposure levels. The study was comprised of two separate experiments: a single 6-h inhalation exposure and repeated inhalation exposures for 3 weeks (6 h per day, 5 days per week). In both experiments, male and female rats were exposed nose-only to aerosol atmospheres of either 0, 1, 10, or 25 mg/m^3 PFOA. In the single exposure experiment, blood was drawn via the tail vein pre-exposure, four times concurrent to exposure, and six times post-exposure up to 24 h. In the repeated exposure experiment, blood was collected immediately before and after exposure 3 days per week. Plasma PFOA concentrations were quantitated by liquid chromatography–mass spectrometry (LC–MS). Following the single exposures, plasma PFOA concentrations were directly proportional to airborne concentrations in both male and female rats. Elimination of PFOA from the plasma was sex-dependent, with female rats eliminating PFOA much more rapidly than male rats. Following repeated PFOA exposure, there was little daily PFOA carryover observed in plasma samples from female rats, while males demonstrated an accumulative pattern over the 3-week period. Peak post-exposure PFOA plasma concentrations in female rats averaged 1, 2, and 4 μg/mL when exposed to 1, 10, and 25 mg/m^3 PFOA, respectively, and returned to baseline levels by the time of the next pre-exposure sample collection. Male rats reached steady state plasma concentrations of 8, 21, and 36 μg/mL (ppm) after 3 weeks of exposure to 1, 10, and 25 mg/m^3 PFOA, respectively. These results demonstrate that the pharmacokinetic properties of inhaled PFOA in male and female rats are similar to those observed in male and female rats following oral dosing with PFOA. It is thus possible to use this internal dose metric (plasma PFOA) for route-to-route dose extrapolation, with inhalation exposures of 1, 10, and 25 mg/m^3 PFOA corresponding to oral doses of approximately 0.3, 1.0, and 2.0 mg/kg in rats.

Keywords: Perfluorooctanoic acid; PFOA; Inhalation exposure; Pharmacokinetics; Rat

1. Introduction

Perfluorooctanoate (PFOA, the perfluorinated analog of octanoic acid) is used as a processing aid in the production of fluoropolymers, typically as the ammonium salt (APFO). The toxicity of PFOA (usually administered as APFO) has been characterized in numerous studies with various animal species. The data on APFO/PFOA can be used interchangeably since, in the presence of water,

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APFO readily dissociates into the PFOA anion. Reviews of APFO/PFOA are available covering the general and developmental toxicity, as well as its pharmacokinetics (Griffith and Long, 1980; Kudo et al., 2002; Kennedy et al., 2004; Lau et al., 2004). PFOA has been identified in sera samples collected from the general populations of Canada, the United States, Europe, and Japan (Olsen et al., 2003a,b; Harada et al., 2004; Kannan et al., 2004; Kubwabo et al., 2004).

Female rats are distinct from male rats in their ability to rapidly excrete PFOA (Hanhijärvi et al., 1982, 1987, 1988; Kemper and Jepson, 2003; Kojo et al., 1986; Kudo et al., 2002; Vanden Heuvel et al., 1991, 1992). Kemper and Jepson (2003) reported that plasma elimination kinetics in non-pregnant, adult female rats appeared to be biphasic after single oral doses of 5 and 25 mg/kg where terminal elimination half-lives were dependent on the dose level and were generally in the range of 2–12 h. Elimination half-lives for male rats following oral dosing of PFOA were approximately 5–10 days (Kennedy et al., 2004). No available inhalation studies include sufficient data on blood PFOA levels to determine appropriate and reliable pharmacokinetic/elimination predictions. Therefore, the objective of this study was to determine the concentration and time relationship between increasing airborne concentrations of PFOA and plasma PFOA levels for the purpose of route-to-route extrapolation using measured blood levels.

2. Materials and methods

2.1. Animal husbandry

Male and female Crl:CD®(SD)IGS BR rats were obtained from Charles River Laboratories, Inc. (Raleigh, NC) and were approximately 6–8 weeks of age at the beginning of the exposures. All rats used on this study were quarantined and acclimated to the facility for at least 5 days prior to any experimental procedures and were weighed and observed for clinical signs of disease during the quarantine period. Rats were housed singly in stainless steel wire mesh cages suspended above cage boards. The animal rooms were maintained on a 12 h light:12 h dark cycle, maintained at 22 ± 1 °C and a relative humidity of 50 ± 20%. Except during inhalation exposures, rats had access to PMI® Nutrition International, LLC Certified Rodent LabDiet® 5002 and water ad libitum. All animal procedures were reviewed and approved by Haskell Laboratory's Animal Welfare Committee.

2.2. Experimental design

2.2.1. Single exposure procedure

Four groups of three male and three female rats each were exposed nose-only for a single, 6-h period to either 0 (air control), 1, 10, or 25 mg/m^3 PFOA. Blood samples were collected pre-exposure at 0.5, 1, 3, and 6 h during exposure, and at 1, 3, 6, 12, 18, and 24 h post-exposure by tail venipuncture. Individual rat exposure times were staggered by 5 min to allow for blood collection. To facilitate a continuous and non-interrupted exposure, restrained rats were situated on the face plate of the exposure chamber in a manner that made the tails accessible for the venipuncture procedure while concomitantly being exposed to test substance. Blood was collected in heparinized tubes and stored on wet ice and subsequently separated by centrifugation with the plasma collected and frozen until analysis.

2.2.2. Repeated exposure procedure

To set the exposure levels for the repeated exposure experiment, plasma concentrations from the single inhalation exposure study as well as previous oral dosing studies in rats were used. Exposure levels yielding plasma concentrations similar to those observed in the oral studies were selected for the repeated inhalation exposure study. Four groups of five male and five female rats each were exposed nose-only for a 6-h period, 5 days per week (weekends excluded), for 3 weeks to an aerosol of either 0 (air control), 1, 10, or 25 mg/m^3 PFOA. Tail venipunctures were performed on all rats before and immediately after the daily exposure period 3 days per week for 3 weeks (on study days 0, 2, 4, 7, 9, 11, 14, 16, and 18).

2.3. Inhalation exposure system

All exposure chambers were constructed of stainless steel and glass with a nominal internal volume of 150 L. Preliminary studies indicated that the airborne concentrations of test substance were uniformly distributed throughout the breathing zone of the rats. Rats were individually restrained in polycarbonate (single exposure) or perforated stainless steel cylinders (repeated exposure) with conical nose pieces. Prior to any experimental procedures, all rats were acclimated to the nose-only restraining cylinders on two separate occasions. During a pilot, difficulty with the venipuncture procedure was encountered. It was determined that the body temperature of the rats was decreasing by ~1–2 °C after a few hours into the exposure period. To facilitate the tail venipuncture and protect personnel from inadvertent test substance exposure, the chambers were placed in chemical fume hood such that the rat tails were situated at the face of the hood. It was determined that the high volume of air flowing over the tails of the rats and their inactivity was contributing to the body temperature decreases resulting in a vasoconstriction of the tail vein. Therefore, to minimize the heat loss, heat lamps were employed to prevent the drop in body temperature. Further pilot work demonstrated that body temperature was relatively constant in this setup and thus body temperature was not monitored during the main studies.

Perfluorooctanoic acid (linear; Aldrich Chemicals, St. Louis, MO) was received as a solid white powder. To facilitate stable concentrations of PFOA and the generation of respirable aerosol in the exposure chambers, the test substance

was dissolved in water (5%, w/w) and buffered with ammonium hydroxide to a pH of 6–8. The 5% (w/w) solution was then used to generate the exposure atmospheres with filtered, high pressure air and a Spraying Systems nebulizer. Chamber concentrations were controlled by varying the infusion rate to the nebulizer and using dilutional air.

During the single exposure experiment, the animals were subject to timed repeated venipunctures during the exposure which precluded use of the cascade impactor for particle characterization. The cascade impactor, and associated pumps and tubing, would have prevented access to the animal's tails.

During the repeated exposure experiment, since the animals were not subject to venipunctures during the exposure, the atmospheric concentrations of PFOA were determined by gravimetric analysis on an hourly basis. Known volumes of atmosphere were drawn from the chamber through a sampling train that consisted of filter cassette containing a 25 mm preweighed glass fiber filter. The PFOA concentration was based upon the pre- and post-sampling filter weights divided by the volume of atmosphere sampled. A preliminary study was performed where filters collected from PFOA chamber concentrations of either 1, 10, or 25 mg/m^3 and blank filters were desiccated for 24 h and reweighed to ensure the gravimetric analysis technique accurately reflected the total mass of PFOA in the exposure atmospheres. Following 24 h of desiccation, all filters lost <0.03% total mass, indicating that the filter mass measured immediately following air sampling reflected the total mass of PFOA in the exposure atmospheres. Samples to determine mass median aerodynamic diameter (MMAD) were taken with a Sierra® Series 210 cascade impactor. Chamber airflows were set to achieve at least 10 air changes per hour and were monitored continuously. Chamber temperature, relative humidity, and oxygen concentration were measured at least twice during each exposure.

2.4. Plasma PFOA determination

Plasma samples were thawed and processed by protein precipitation (PPT) using Isolute Array protein precipitation columns (Argonaut Technologies, Foster City, CA). A 0.5 μg/mL solution of perfluorononanoic acid (Aldrich Chemicals) in acetonitrile (ACN) was used as an internal standard. Plasma samples (20 μL aliquots) were applied to the PPT array and were precipitated by adding appropriate dilution rate volumes of ACN/internal standard solution. Dilution rates, ranging from 1:4 (60 μL of internal standard solution) to 1:50 (980 μL of internal standard solution), were utilized in order to capture the sample concentrations within the range of the standard curve concentrations. The array was slowly eluted under vacuum into a 96-well receiver plate, centrifuged at ~3000 rpm for 5 min and the extracts recovered. Aliquots of the extract were injected into a Waters 2790 Liquid Chromatograph equipped with a Waters Xterra MS C18 column and a Quattro Micro Mass Spectrometer detector. Plasma levels are reported as ppm (μg/mL).

2.5. Statistical analysis

Plasma concentrations (female post-exposure weeks 1–3; male post-exposure week 3) were compared using a single factor ANOVA test with significance judged at $p < 0.05$.

3. Results

3.1. Single exposure

The mean atmospheric concentrations for the three exposure groups were all within 20% of the targeted concentrations (Table 1). Due to the multiple tail venipunctures concurrent to exposure, the aerosol size for the single exposure experiment was not measured. However, preliminary measurements of test atmospheres at similar concentrations prior to animal exposures demonstrated mass median aerodynamic diameters (MMADs) that ranged from 1.9 to 2.1 μm and aerosols were shown to be respirable under identical generation conditions (1.4–2.0 μm MMAD) used in the repeated exposure study (Table 3). For all the exposure chambers, the mean temperature ranged from 24 to 26 °C, the mean relative humidity ranged from 34 to 40%, the airflow into the chambers ranged from 27 to 70 L/min (lpm), and the mean oxygen concentration was 21%.

For both sexes, PFOA plasma concentrations rose during the 6-h inhalation exposure. A proportional relationship was produced in both the male and female rats with maximal PFOA plasma concentrations (C_{max}) between 1 and 25 μg/mL (Fig. 1). The male C_{max} values were approximately two to three times higher than that observed in females. The female C_{max} occurred between the end of the exposure period and 1 h post-exposure while the male C_{max} occurred between 0 and 6 h post-exposure. Elimination of PFOA from female rat plasma was rapid and complete at all exposure levels where plasma concentrations dropped below the analytical limit of quantification (0.1 μg/mL) by 12 h post-exposure. Plasma elimination was slower in male rats, with plasma concentrations approximately 90% of the

Table 1
Chamber concentrations from single PFOA exposure study

Design concentration (mg/m^3)	Measured concentration (mean ± S.D.) (mg/m^3)	Range (mg/m^3)
1	1.2 ± 0.38	0.66–1.7
10	9.8 ± 0.58	9.0–11
25	27 ± 3.1	24–32

Results represent the mean ± standard deviation (S.D.) and range; $n = 6$.

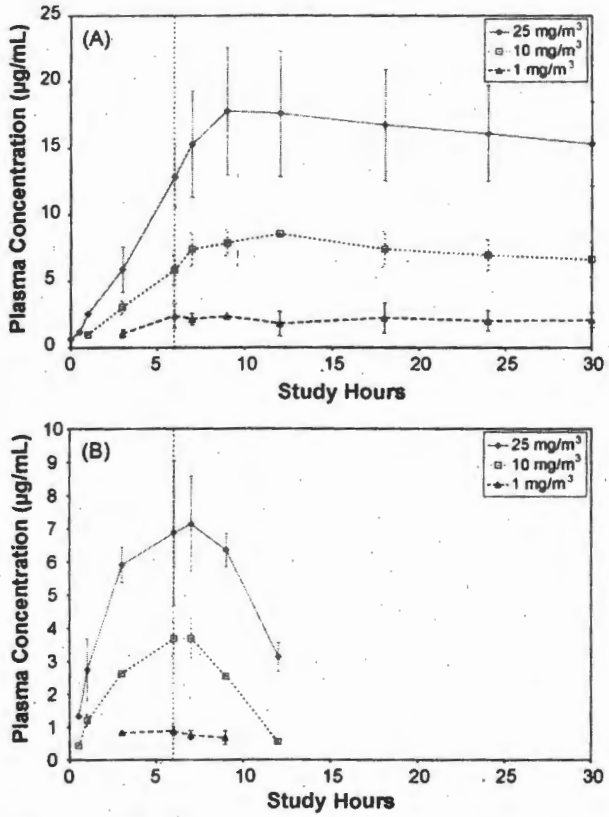

Fig. 1. Plasma PFOA concentrations in male (Panel A) and female (Panel B) rats exposed to 1 mg/m^3 (▲), 10 mg/m^3 (□), or 25 mg/m^3 (♦) PFOA for 6 h. Results represent the mean ± S.D., n = 2–3. *Note:* The dashed vertical line denotes the end of the exposure.

peak concentrations at 24 h post-exposure in all tested exposure levels. In addition, the elimination rate was not concentration dependent in either male or female rats as the plasma concentration curves are semi-log parallel. To set exposure levels for the repeated exposure study, male and female C_{max} values were compared to plasma C_{max} from an oral gavage study of PFOA (Kemper and Jepson, 2003). In that study single oral gavage doses from 0.1 to 25 mg PFOA/kg body weight produced C_{max} values ranging from 0.60 to 160.0 µg/mL (male) and 0.67 to 132.7 µg/mL (female). Because the C_{max} values from the single exposure study fell within the range of the oral gavage data, the exposure concentrations were not changed for the repeated inhalation exposure study.

3.2. Repeated exposure

The mean atmospheric concentrations for the three exposure groups were all within 10% of the targeted concentrations (Table 2). The aerosol size characteristics of the three exposure levels ranged from 1.4 to 2.0 µm

Table 2
Chamber concentrations for the repeated PFOA exposure study

Design concentration (mg/m^3)	Measured concentration (mean ± S.E.M.) (mg/m^3)	Range (mg/m^3)
1	1.1 ± 0.04	0.81–1.13
10	10 ± 0.11	9.4–11
25	25 ± 0.43	21–27

Results represent the mean ± standard error of the mean (S.E.M.) and range of the average daily chamber concentrations; n = 15.

Table 3
Aerosol size analysis of PFOA exposure atmospheres

Design concentration (mg/m^3)	MMAD ± G.S.D.
1	1.7 µm ± 1.6
10	1.4 µm ± 2.0
25	2.0 µm ± 1.8

Results represent the mean mass median aerodynamic diameter (MMAD) ± geometric standard deviation (G.S.D.) of three samples collected from each exposure chamber.

MMAD with geometric standard deviations that ranged from 1.6 to 2.0 indicative of a log normal distribution (Table 3). The overall mean temperatures for all the exposure chambers ranged from 24 to 25 °C, the mean relative humidity ranged from 33 to 39%, the airflow into the chambers ranged from 28 to 70 lpm, and the mean oxygen concentration was 21%.

Repeated exposure plasma concentrations are shown in Fig. 2. The male and female concentration curves demonstrate the effects of the sex-specific elimination kinetics on plasma levels following repeated exposure. In the female rats, there was little day-to-day carryover of PFOA in the plasma. There is no significant difference between the peak heights of the sampled exposure days ($p < 0.05$). For the male rats, there is carryover between test days as expected from the single exposure. By week 3, the periodic peak concentrations reached a steady state with plasma concentrations of approximately 8, 21, and 36 µg/mL for 1, 10, and 25 mg/m^3, respectively. These steady state values are approximately two to three times higher than the C_{max} values from the single exposure experiment of approximately 2.4, 8.8, and 17.8 µg/mL for exposures of 1, 10, and 25 mg/m^3, respectively. As in the single inhalation exposure, repeated exposures demonstrate a proportional relationship between exposure and plasma concentrations in male and female rats.

4. Discussion

In female rats, excretion of PFOA was rapid such that no accumulation in plasma was seen in any of the

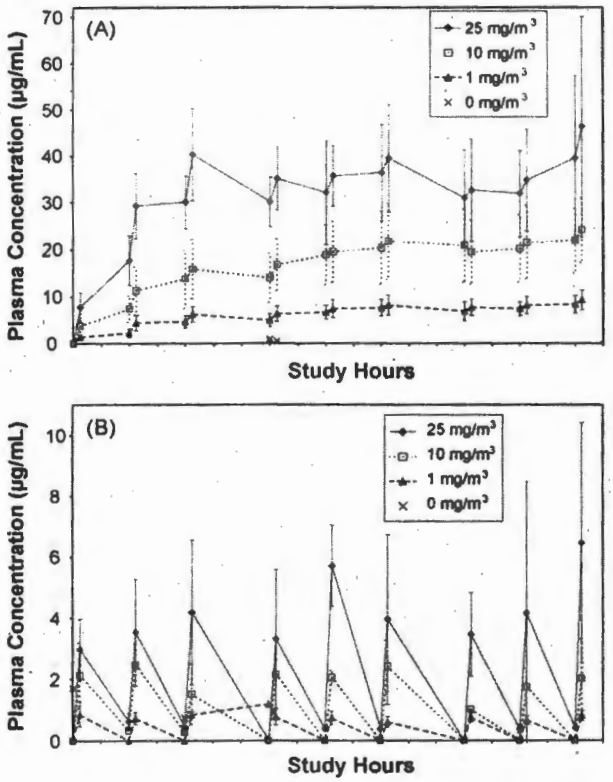

Fig. 2. Plasma PFOA concentrations in male (Panel A) and female (Panel B) rats exposed to 0 mg/m^3 (×), 1 mg/m^3 (▲), 10 mg/m^3 (□), or 25 mg/m^3 (♦) PFOA 6 h per day, 5 days per week for 3 weeks. Sampling occurred on study days 0, 2, 4, 7, 9, 11, 14, 16, and 18. Results represent the mean ± S.D., $n = 5$. *Note:* The lines connecting the data points are included for visual clarity and do not indicate actual concentrations.

pre-exposure samples taken during the 3 week repeated exposure. Post-exposure concentrations from the first week ranged from 3 to 4 μg/mL, the second week from 4 to 6 μg/mL, and the third week from 4 to 7 μg/mL. Statistical analysis indicates that very little, if any, residual serum PFOA is present when the subsequent daily exposures occur. The pre- and post-exposure PFOA concentrations do not change appreciably during the experiment and appear to represent a series of acute exposures in which the serum carryover from previous exposures is minimal.

For male rats there was an increase in pre- and post-exposure serum PFOA levels during each week at each exposure concentration. Using the 25 mg/m^3 group as an example: in week 1, the mean post-exposure concentrations increased from 8–30 to 38 μg/mL; in week 2, the corresponding values were 35, 37, and 44 μg/mL; and in week 3, values were 34, 37, and 46 μg/mL (days 1, 3, and 5, respectively). The last post-exposure value (46 μg/mL) was the highest mean value recorded and might suggest that the PFOA serum levels are not at a steady state. However, this point was not statistically different from the other week 3 post-exposure points ($p < 0.05$). The concentration profiles in the rats exposed to either 1 or 10 mg/m^3 also suggest that these rats have either reached or are close to steady state.

The relationship between external dose and internal dose is helpful in assessing data from multiple routes of exposure. The determination of no-observed effect and low-observed effect levels (NOEL and LOEL, respectively) can be linked to internal dose, i.e. exposure concentration and plasma levels. NOEL's and LOEL's for PFOA have been established in both rodents and primates in multiple extended dose studies by the oral route (Butenhoff et al., 2004). In these oral experiments, plasma PFOA levels were measured as an internal marker of dose. For the inhalation route of exposure, longer term animal experiments are not available, the longest being a 24 day repeated-exposure rat study (Kennedy et al., 1986). Although Kennedy et al. (1986) did determine both NOEL and LOEL exposure levels, the lack of blood PFOA concentrations at different time points limits its usefulness for examining pharmacokinetic properties. By relating external inhaled PFOA concentration to plasma PFOA, under both acute and steady state conditions, internal dose metrics can link descriptive inhalation toxicity results to toxicity end-points derived from longer term studies by other routes, specifically oral.

In the current study, inhalation of atmospheric PFOA concentrations of either 1, 10, or 25 mg/m^3, for 6 h per day, 5 days per week for 3 weeks by male rats resulted in steady state post-exposure (average post-exposure for the third week) plasma PFOA levels of 8, 21, and 36 μg/mL, respectively. To correlate with end-point specific external APFO doses, determinations or estimates of internal plasma PFOA concentration were made from a series of repeated dose oral studies, including a 13-week dietary study in rats, a 6-month oral toxicity study in monkeys, a 2-year oral study in rats, and a two generation reproduction study in rats, where end-points such as liver weights, body weight changes, post-natal development, and Leydig cell tumors were used. Using the inhalation–oral concentration relationship to bridge from end-points derived from oral studies would allow estimates of inhalation conditions which would be expected to produce similar effects/non-effects. For example, 1 mg/m^3 produced no-observed adverse effects in rats following a 2-week inhalation exposure, corresponding to a steady state plasma PFOA level of approximately 10 μg/mL. The kinetics of PFOA following inhalation exposure is similar to those reported following oral exposure (Kemper and Jepson, 2003). The plasma half life is

approximately 3 h in females and greater than 1 day in males, as determined from the single exposure experiment. The repeated exposure experiment is consistent with this observation but was not designed for calculation of half-lives.

By knowing the blood level of PFOA following known external dose(s), we can accomplish meaningful route-to-route extrapolations. In this case, we have determined steady state plasma levels in male rats following multiple inhalation exposures of 8, 21, and 36 μg/mL PFOA (inhalation exposures of 1, 10, and 25 mg/m^3 PFOA, respectively). The same steady state blood levels of PFOA can be compared in male rats following oral doses of approximately 0.3, 1, and 2 mg/kg body weight. This approximates a 10-fold difference, i.e. it is predicted that a 1 mg/kg oral dose produces the same PFOA blood level as a 10 mg/m^3 inhalation exposure in rats. Based on the plasma concentrations reported here, inhalation exposures of 1, 10, and 25 mg/m^3 PFOA correspond to oral doses of 0.27, 0.96, and 2.0 mg/kg in rats.

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